FOOD AND DRUG ADMINISTRATION
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS – HFD-550

Medical Officer Review

VIOXX
(Rofecoxib)

NDA 21-042 (capsules) and NDA 21-052 (oral solution)

Submission date (letter):	November 23, 1998.
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Reviewer:	Maria Lourdes Villalba, MD.
Drug name:	VIOXX (Rofecoxib)
Applicant:	Merck Research Laboratories
Pharmacologic category:	NSAID (COX-2 inhibitor)
Proposed indications:	Management of acute pain, dysmenorrhea and signs and symptoms of osteoarthritis.
Dosage form and route:	Oral capsule, 12.5 and 25 mg Oral solution 12.5 mg/5ml and 25 mg/5ml
CSO:	Sandra Cook

Orig NDA # 21042
HFD-550/Div File
HFD-550/PM/Cook
HFD-550/Pharm/Wilson
HFD-550/Chem/BHo
HFD-880/Biopharm/DBaswhaw
HFD-550/Statistics/SLin/QLi
HFD-550/MO/JHyde/JWitter
HFD-550/MO/KJohnson
HFD-550/MO/MLVillalba

/S/ 5/20/99
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/S/ 5-26-99
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Executive summary

Rofecoxib is efficacious in the treatment of the signs and symptoms of osteoarthritis (OA) at the proposed doses (12.5 and 25 mg/day).

The results of the single dose analgesic efficacy of Rofecoxib are robust enough to recommend its approval at the proposed dose (50 mg single dose).

The overall safety profile of Rofecoxib at the proposed doses was similar to comparator NSAIDs. Some data (study 029) suggest that Rofecoxib 50 mg QD may be more effective than 25 mg QD in OA. However, with chronic administration of ≥ 50mg QD (studies 044 and 045), the data suggest an increased risk of developing adverse events, particularly renal and gastrointestinal (GI) adverse events.

The applicant is not seeking approval for the indication of treatment of signs and symptoms of rheumatoid arthritis (RA) at this time.

Relevant issues:

1) **Dose-response and maximum effect in analgesia and osteoarthritis studies.**

   In one pivotal dental pain study (071) Rofecoxib 100 and 200 mg doses were significantly more effective than the 50 mg dose. Also, 50 mg appeared to perform better than 25 mg in a multi-dose acute analgesia study (post-orthopedic surgery).

   In a randomized, double blind, placebo controlled six-week dose ranging study (029), the data suggested that Rofecoxib 50 mg QD was more efficacious for OA than the proposed doses. However, in 6-month trials designed to assess GI and general safety (044 and 045) this dose was found to be associated with a numerical increase of general GI, endoscopic and renal related adverse events.

2) **Duration of rofecoxib analgesic effect**

   Although Rofecoxib showed statistical analgesic superiority over placebo for 24 hours following a single dose administration, the available data for later time points were less robust.

3) **Gastrointestinal safety.**

   In taking into consideration all GI safety parameters, Rofecoxib does not appear to be the same as placebo. Additionally, chronic dosing at 50 mg QD was associated with numerically more clinical GI adverse events and endoscopic ulcers compared to 25 mg QD.

4) **Effects in acid-base balance.**

   Because serum Bicarbonate and Chloride were measured in only two studies, an adverse effect of Rofecoxib on acid-base balance can not be excluded.

Background and overview.

Currently available nonsteroidal anti-inflammatory drugs (NSAIDs) have been characterized as dual COX-1/COX-2 inhibitors and their toxicity represents a significant source of morbidity and mortality in the treatment of arthritis and other inflammatory disorders.

Rofecoxib (VIOXX™) also known as MK-0966, is a NSAID that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models. The mechanism of action of rofecoxib is thought to be due to inhibition of prostaglandin synthesis via inhibition of Cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans rofecoxib does not inhibit the Cyclooxygenase-1 (COX-1) isoenzyme.

Based on the pattern of localization and induction of COX-1 and COX-2 enzymes (COX-1 = constitutive, COX-2 = inducible), it was initially hypothesized that COX-1 would be the isoform responsible for the physiological functions of prostanoids including gastric mucosal protection and vascular homeostasis and COX-2 would be primarily responsible for the synthesis of prostanoids in pathological processes such as inflammation, pain and fever. The great advantage of a selective COX-2 inhibitor would be to be effective without the toxicity associated with inhibition of COX-1 derived prostanoids that mediate homeostasis. It is now known that the picture is not that simple. COX-2 is constitutively expressed in several tissues (brain, testes, kidney, pancreas, human amnion and reproductive system) and COX-1 is also inducible (although modestly) during inflammation.

It is now believed that some of the adverse events observed with non selective NSAIDs, are related, at least in part, to COX-2 inhibition. Based on the adverse event profile of Celecoxib and previous NSAIDs, this review will focus on the potential adverse effects of Rofecoxib on renal function, GI bleeding, platelet function, pancreas, acid base balance and reproductive system, in addition to considering the usual efficacy and general safety concerns.

The applicant is applying for the use of Rofecoxib in the following indications:

1) For acute and chronic treatment of the signs and symptoms of osteoarthritis
2) For the relief of acute pain
3) For treatment of primary dysmenorrhea.

The applicant is not applying for the indication of the treatment of the signs and symptoms of RA at this time. Data from two completed clinical studies in RA (one 6-week Phase II study and its extension) have been submitted in the original NDA.

A total of 58 trials were submitted to support NDA 21-042 (tablet formulation). Those studies are presented in Table 1. The same studies support NDA 21-052 (oral solution).

Table 1. Studies included in NDA 21-042/52

Phase I studies/clinical pharmacology		
11 Single dose, 13 Multiple dose, 10 Interaction studies, 3 Renal impairment studies, 1 single dose Hepatic impairment study, 2 special GI studies		
Osteoarthritis	number	duration
Phase II	2	6 weeks
Phase III	3	6 weeks
	2	1 year
	4	Extension studies (6 months to 86 weeks)
	2	6 months (endoscopic studies)
Rheumatoid Arthritis		
Phase II	1	6 weeks
	1	Extension study (up to 30 weeks)
Analgesia studies		
	4	Dental pain
	3	Dysmenorrhea
	1	Orthopedic pain

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The Clinical Review of this NDA is divided into six sections:

- Osteoarthritis Efficacy (Maria Lourdes Villalba, M.D.)
- Overview of Rofecoxib Safety (Maria Lourdes Villalba, M.D.)
- Acute Pain and Dysmenorrhea. Efficacy and Safety (Mordechai Averbuch, M.D.)
- Gastrointestinal Safety (Larry Goldkind, M.D.)
- Renal Safety (Juan Carlos Pelayo, M.D.)
- Hematology Safety (Ann Farrell, M.D.)

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1 - OSTEOARTHRITIS EFFICACY REVIEW

Thirteen studies (nine base studies and four extensions) were conducted to assess the efficacy and safety of rofecoxib in patients with osteoarthritis of the knee or hip (Table 2). Large part of this efficacy review will focus on studies **010** and **029** (Phase II studies) and the rationale for dose selection for phase III studies in OA. To demonstrate the efficacy of rofecoxib in OA, four pivotal studies were submitted to this NDA: two 6-week placebo and active-comparator [ibuprofen] controlled studies (**033** and **040**) and two one-year active-comparator [diclofenac] controlled studies (**034** and **035**). Study **058** evaluated the effects of rofecoxib in the elderly. The extension studies (**29-10, 29-20/30, 34-C** and **58-10/20**), as well as the endoscopic studies (**044** and **045**) provide more safety than efficacy data but relevant efficacy data will be included in this part of the review.

An overview of the OA efficacy program will be followed by a discussion of dose selection and analyses of results of individual studies.

1.1. OVERVIEW OF EFFICACY IN OA

1.1.1.Study characteristics

All studies in the rofecoxib OA program were multi-center, randomized, double-blind, controlled, parallel studies in patients with OA of the knee or hip. Patients were required to have a history of positive benefit with NSAIDS and met a "flare criteria" after a pre-specified washout period. Pivotal trials also included up to 20 % of patients who were acetaminophen users (not NSAIDS-users). Study 058, 044 and 045 were "non flare" studies.

The six-week trials (including two of the pivotal studies) were placebo-controlled; the one-year pivotal trials did not include a placebo arm. Doses of rofecoxib used in most trials were 12.5 and 25 mg QD, except trial 010 (pilot) that studied rofecoxib 25 and 125 mg QD. Study 029 (dose ranging) explored the doses of rofecoxib 5, 12.5, 25 and 50 mg QD. Doses of NSAIDs used in active-comparator-controlled studies were: ibuprofen 800 mg TID (033, 040, 044 and 045); diclofenac 50 mg TID (034,035 and extensions to 029) and nabumetone 1500 mg/day (058 and 058-10). Two studies provide data on rofecoxib 50 mg QD for 6 months (044 and 045).

Table 2. Study characteristics. All Rofecoxib Osteoarthritis Controlled Trials.

Study #	Duration	Number of Centers	Characteristics	Placebo n	(Rofecoxib dose, mg/day) n					Comparators n			Total
					5	12.5	25	50	125	Ibu [3]	Diclo [4]	Nab [5]	
Phase II													
010	6 weeks	27 US	R, DB, PC (knee only)	72			73		74				219
029		64 US	" " "	145	149	144	137	97					672
Phase III													
033 *	6 weeks	62 US	R, DB, PC & AC	69		219	227			221			736
040 *		52 non-US	" " " "	74		244	242			249			809
058		45 US	" " " " in elderly †	52		118	56					115	341
034 *	6 months[1]	43	R, DB, AC			231	232				230		693
035 *		69 US	" " "			259	257				268		784
029-10	6 wk - 6mo	51 US	R, DB, AC			104	148				215		467
029-20	6 mo-1 year		" " "			63	86	75			62		286
029-30	1 year-18mo		" " "			47	62	54			48		211
034-10	6 mo-86 wk	112 (69 US	R, DB, AC	}		224	218				215		657
035-10		& 43 non-US)		}									
058-10	6 wk - 6 mo	41 US	R, DB, AC in elderly			81	37					78	196
044	6 months[2]	34 US	R, DB, AC, endoscopic†	177			195	186		184			742
045		5 US, 31 non-US	" " " " †	194			195	193		193			775
All[6]				783	149	1215	1614	476	74	847	397	115	5771

- Pivotal trials. † "Non-flare" studies. n – number of patients randomized. 1- Studies 034 and 035 were designed as one year trials; data from these studies was analyzed separately up to 6 months and pooled for analysis for the second six month of the year and the extensions. 2- These were identical 12 week studies with a 12 week extension. 3- Ibu: ibuprofen 2400 mg/day. 4- Diclo: diclofenac 150 mg/day. 5-Nab: nabumetone 1500 mg/day. R: randomized. DB: double-blind. PC: placebo controlled. AC: Active comparator controlled. 6- Some patients may have received more than one treatment.

Eligibility/exclusion criteria

Following are relevant criteria regarding efficacy. (From protocol 029. Differences will be mentioned where appropriate).

Inclusion criteria:

1) Male or female, at least 40 years of age, with a clinical diagnosis of OA of the knee or hip based on clinical and radiographic criteria and symptoms present for at least 6 months prior to study entry. Patient assessment of Pain Walking On A Flat Surface (WOMAC Section A, Question 1) at the Pre-study Visit, less than 80 mm (on a 100-mm VAS).

2) History of positive therapeutic benefit with NSAIDs in the past. Patient was taking a NSAID on a regular basis (>25/30 days) at a therapeutic dose level for at least 30 days prior to study enrollment. Prior to randomization and following the discontinuation of the patient's prior NSAID therapy according to a pre-specified schedule or "washout period" (Appendix A.1) at "Flare/Randomization Visit"(Visit 2) patient satisfied all three of the following FLARE criteria :

a) Minimum 40 mm on patient-reported WOMAC Pain Walking on a Flat Surface.
b) Increase 15 mm on patient-reported WOMAC Pain Walking on a Flat Surface compared with pre-study baseline recorded at Visit 1.
c) Worsening in Investigator Global Assessment of Disease Status of at least 1 point on a 5-point Likert scale compared with the pre-study baseline recorded at Visit 1.

Exclusion criteria: Previous/Concurrent Medication

Patients who had received intravenous or intramuscular corticosteroids or intra-articular steroids to a joint other than the study knee or hip within 1 month of entry to the study; oral corticosteroids, intra-articular steroids to the study knee or hip, or other immunosuppressant medication within 3 months of entry into the study.

In pivotal trials, patients who were "acetaminophen users" needed to satisfied the following criteria (at both Visit 1 [screening] and 2 [randomization visit]).

a) Minimum 40 mm on patient-reported WOMAC Pain Walking on a Flat Surface
b) Investigator Global Assessment of Disease Status as "fair," "poor," or "very poor" (Likert Grades 2, 3, or 4, respectively)
c) Minimum 40 mm on Patient Global Assessment of Disease Status (100-mm VAS).

Acetaminophen users did not require a worsening in evaluation between visit 1 and 2. They were able to continue taking acetaminophen as a rescue medication during the study, but needed to discontinue use at least 48 hours prior to any evaluation of clinical efficacy. Patients were stratified as NSAID or acetaminophen users.

Reviewer's note: Most of the patients at entry were well above the minimum criteria of 40 mm in WOMAC Pain Walking on Flat surface. For "flare" studies the mean score at entry was above 74 ± 15 mm, however for study (058 ("non-flare"study), the mean score at entry was 55 ± 25 mm.

1. Demographics (Appendix A.2)

Baseline demographics and patient characteristics analyzed in these trials included: Age, Gender, Race, Height, Weight, Duration of OA, ARA functional Class (I,II,II), prior NSAID use, History of Ulcer or Upper GI bleeding, study Joint (hip or knee) , baseline values of efficacy end points, secondary diagnoses, prior medications, and concomitant diseases and medications. Most patient were Caucasian women on their 60's with an average of 10 years history of osteoarthritis (except in study 058, where age was>80 and had 15 years of disease). In general, there were no outstanding differences in baseline characteristics among treatment groups within a study. Differences will be mentioned when appropriate. Of note, the mean weight of patients enrolled in US studies was significantly higher than in multinational studies (040, 035 and 045) (10 to 14 kg difference).

2. Efficacy endpoints

The majority of the studies measured several efficacy endpoints. (Listing of endpoints: Table 3, description of endpoints: Appendix A.3.1). However, the designation as to primary or secondary was not consistent among trials (Table 4).

Table 3. End points measured in Rofecoxib Osteoarthritis Clinical Trials*

Efficacy endpoints	
Primary	
	WOMAC Pain Walking in flat surface [1]
	Patient Global of Response to Therapy[2]
	Investigator Global of Disease Status[2]
Key Secondary	
	WOMAC Physical Function Subscale[1]
	WOMAC Stiffness Subscale [1]
	Pt Global of Disease Status[1]
	Discontinuation due to Lack of Efficacy (%)
Other	WOMAC Pain Subscale[1]
	Investigator Global of Response to Rx[2]
	WOMAC Total Score Average[1]
	WOMAC Average Subscale [1]
	Joint Swelling
	Joint Tenderness
	Acetaminophen Use.
Patient Global Assessment of Arthritic Pain [1 3], SF-36 [4], Joint X-ray [5]	

*Designation as to primary or secondary only in study 029 and pivotal trials 033, 040, 034, 035)
1-VAS: 0 to 100 visual analog scale. 2- Likert 5 point scale (0 to 4). 3- PtGAp was a primary endpoint only for study 010. 4- SF-36 was measured only in studies 029 and 058. 5- X-ray were considered efficacy endpoints only for study 034 and 035.

As seen in Table 4, WOMAC Pain Walking on a Flat Surface was a primary endpoint for study 029 and all pivotal trials, along with Investigator Global of Disease Status and Patient Global of Response to Therapy. For studies 058 and 58-10, Patient Global Assessment of Disease Status was the single primary endpoint; the WOMAC questionnaire, Investigator Global Assessment of Disease Status, SF-36 and Joint exam were performed but not defined as primary or secondary. Patient Global Assessment of Disease Status was a secondary endpoints for all the pivotal trials and for study 029.

Most of the efficacy endpoints measured in the rofecoxib OA clinical program are widely validated. However, it is not clear why only one of the five questions of one of the sections of the WOMAC questionnaire was selected as primary endpoint. Experts caution against using only one of the five questions of the Pain Subscale questionnaire because it may not reflect what happens with other aspects of pain (for instance pain at night or pain when climbing stairs). The complete WOMAC Pain Subscale (five questions) was considered a co-primary endpoint for study 010, but a secondary endpoint for all pivotal trials and one of the "other endpoints" in study 029.

Table 4. Controlled trials. Number of patients randomized and main efficacy endpoints measured in each protocol.

Duration	Study #	N	Primary End points	Key Secondary End points
6 weeks	010	219	WPS PtGAp	WPfs PtGR InvGDs
	029	672	WPfs PtGR InvGDs	WFS PtGDs WSS DLOE
	033*	736	" " "	WPS " " " "
	040*	809	" " "	WPS " " " "
	058	341	PtGDs	Several measured but not defined as primary or secondary
6 months	034 *	693	WPfs PtGR InvGDs	WPS WFS PtGDs WSS DLOE
	035 *	784	" " "	" " " " "
Extension studies	029-10	467	" " "	WFS PtGDs WSS DLOE
	029-20	286	" " "	
	029-30	211	" " "	
	034-10		WPfs InvGDs	WPS WFS PtGDs WSS DLOE
	035-10	657	" "	" " " " "
	058-10[1]	196	PtGDs	Several measured but not defined as primary or secondary
6 month endoscopy studies	044	742	Endoscopic	PtGDs
	045	775	"	

* Pivotal studies. N = patients randomized. **WPS** = WOMAC Pain Subscale. **PtGAp** = patient global assessment of arthritic pain. **WPfs** = WOMAC pain walking on flat surface. **PtGR** = Patient Global assessment of Response to therapy. **InvGDs** = Investigator Global assessment of Disease Status. **PtGDs** = Patient Global assessment of disease status. **WFS** = WOMAC Physical Function subscale. **DLOE** = discontinuation due to lack of efficacy. **WSS** = WOMAC Stiffness subscale.

3. Schedule of efficacy assessments

Assessments were done at screening, prior to dosing (flare/randomization visit), and at treatment week 2 and week 6. For 6 month studies, assessments were done at 2, 4, 8, 12, and 26 weeks. For longer than 6 month studies (033 and 034), efficacy assessments were repeated at weeks 39 and 52 (Appendix A.4: schedule of clinical observations).

4. Population analyzed/statistics

The primary analysis was an intent-to-treat (ITT) approach as defined by the applicant. This ITT analysis excluded those patients who had a missing baseline or who were missing all post-study data for that particular end point. Since the number of patients included in the ITT was often lower than the number of randomized patients, the term "evaluable for modified ITT" or just "evaluable patients" will be used in this review.

Primary analyses were based on determination of Least Square (LS) Mean changes in efficacy endpoints from baseline. Most of these analyses were ***averaged over*** the treatment period (as opposed to ***at the end*** of the treatment period, used only in study 058). Secondary analysis included a Per Protocol analysis (PP). The PP approach included all patients with a baseline and at least 1 post-baseline measurement remaining after exclusions due to protocol violations. Also as a secondary analysis, patients who had "good or excellent" responses in three out of three primary endpoints were defined as patients with "consistent clinical response".

> ***Reviewer's comment: Unless noted otherwise, comments in this review will refer only to the ITT modified approach averaged over the treatment period. With this approach, because of comparisons are done based on average changes among patients who continued in the studies, frequent evaluations at the beginning of the studies contribute heavily to the average values.***

1.1.2. Criteria of Comparability to NSAIDs:

In the NDA submission the following two conditions were defined as necessary for two treatments to be considered "clinically comparable":

(1) For any two of the three primary end points the 95% CIs of mean differences between treatment groups were within ±10 mm on a 100-mm VAS or ± 0.5 on a Likert scale.

(2) For each primary end point, the posterior probability that the true mean difference is within the respective predefined clinical comparability bounds was >0.950.

For purposes of demonstrating comparability between a pair of treatment groups for an individual end point, a 95%CI for the mean difference between the groups was compared with predefined "clinically important comparability bounds". If the CI fell within the bounds, the conclusion of comparability between the 2 treatments was drawn.

Reviewer's comment:

During pre-NDA negotiations the Agency accepted the clinical criteria of comparability to NSAIDs proposed by Merck. There was no pre-agreement on the definition of clinical important superiority to placebo. The selected comparability bounds (±10 mm [on a 100-mm VAS] and ± 0.5 [on a 0 to 4 point Likert scale]) are more conservative (i.e., narrower) than the ones determined by a panel of expert rheumatologists as representing clinically meaningful differences (± 17 mm for VAS, ± 0.75 for Likert). Reference: Bellamy N et al, Setting the Delta for Clinical Trials (in OA) – Results of a Consensus Development (Delphi) Exercise (Journal of Rheumatology, 1992).

In a pre-NDA meeting on May 1996 the Agency had stated that three out of three (not two out of three) primary endpoints needed to be successful. Three out of three is the criterion pre-established in all protocols and the one used for the analyses.

1.1.3. Efficacy Results.

Superiority to placebo: All five placebo-controlled six-week studies showed that rofecoxib at the doses of 5 to 125 mg a day was **statistically significant different from placebo.**

Reviewer's comment: Table 5 shows the difference in LS Mean changes from baseline for rofecoxib and active comparators compared to placebo for primary efficacy endpoints. For WOMAC Pain Walking on a Flat Surface the differences between active treatments and placebo in pivotal trials (033 and 040) ranged from –12.5 to –16.5 mm (VAS). It could be argued that a minimum difference of 15 mm should be required to establish superiority to placebo (this was the minimum change in WOMAC Pain Walking on a Flat Surface required for a patient to be eligible to enter the pivotal studies).

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Table 5. LS mean changes from baseline averaged over 6-week period for efficacy endpoints in placebo-controlled OA trials.

Study # and characteristics		WOMAC Pain Walking on Flat (100 mm VAS)		Investigator Global Assessment of Disease Status (0 to 4 Likert)		Patient Global of Response to Therapy (0 to 4 Likert)	
	n	LS Mean change	Difference vs. placebo	LS Mean change	Difference vs. placebo	LS Mean change	Difference vs. placebo
010 – Pilot. R, DB, PC							
Placebo	70	-6.8	-	-0.5	-	-1.3	-
Rofecoxib 25 mg/d	73	-26.0	-19.2*	-1.5	-1.0*	-2.3	-1.3*
Rofecoxib 125 mg/d	74	-29.0	-22.2*	-1.6	-1.1*	-2.8	-1.5*
029 – Dose ranging R, DB, PC							
Placebo	139	-17.5	-	-0.7		-1.2	-
Rofecoxib 12.5 mg/d	147	-31.8	-14.3*	-1.4	-0.7*	-2.3	-1.0*
Rofecoxib 25 mg/d	143	-33.0	-15.5*	-1.4	-0.7*	-2.3	-1.1*
Rofecoxib 50 mg/d	97	-41.1	-23.6*	-1.7	-1.3*	-2.6	-1.3*
033 – R, DB, PC & AC							
Placebo	69	-17.2	-	-0.8		-1.4	
Rofecoxib 12.5 mg/d	218	-29.6	-12.4*	-1.4	-0.6*	-2.2	-0.9*
Rofecoxib 25 mg/d	222	-33.7	-16.5*	-1.5	-0.7*	-2.4	-1.1*
Ibuprofen 2400 mg/d	218	-30.7	-13.5*	-1.4	-0.5*	-2.3	-0.9*
040 – R, DB, PA & AC							
Placebo	74	-18.9	-	-1.0	-	-1.5	-
Rofecoxib 12.5 mg/d	243	-34.3	-15.4*	-1.5	-0.5*	-2.3	-0.7*
Rofecoxib 25 mg/d	237	-35.1	-16.2*	-1.6	-0.6*	-2.5	-0.9*
Ibuprofen 2400 mg/d	247	-33.6	-14.6*	-1.4	-0.4*	-2.2	-0.7*
058 – Elderly. R, DB, PC & AC						Patient Global of Disease Status †	
Placebo		-4.3		0.4		-12.7	
Rofecoxib 12.5 mg/d		-13.1	-9.0**	-0.8	0.4**	-25.7	-13.0*
Rofecoxib 25 mg/d		-14.9	-10.7**	-0.9	-0.4**	-25.0	-12.3*
Nabumetone 1500 mg/d		-14.3	-10.0**	-0.8	-0.3**	-25.0	-12.3*

• $p < 0.001$. ** $p < 0.05$. † This was the single primary efficacy endpoint (100 mm VAS).

If we were to use the criteria of clinical comparability to NSAIDs defined by the applicant to compare the differences in LS Mean changes from baseline between placebo and active treatments, the differences were above the range of comparability. If we were to use the criteria suggested by Bellamy et al (± 17 mm in a VAS or 0.75 in a 5 point Likert scale), rofecoxib and ibuprofen would have been within the range of clinical comparability with placebo.

Of note, in study 058, the differences between active treatments and placebo for WOMAC Pain Walking and Investigator Global of Disease Status were statistically different but very close or within the range of clinical comparability as defined by the applicant.